The Influence of Noise in Cytotoxicity Assessment

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Introduction

Many chemicals produced by industrial activity might be hazardous to human health or the environment. Rather than conducting expensive and sometimes contentious in vivo assays, we might try using mathematical or computational models to assess the effect of toxicants on human cells.

At the Alberta Centre of Toxicology, time-dependent response curves (TCRCs) were generated from in vitro assays using the xCELLigence Real-Time Cell Analysis HT system. The toxicants are grouped in 10 clusters, according to the mode of action. The goal of this study is to find a mathematical model that could accurately reproduce these curves.

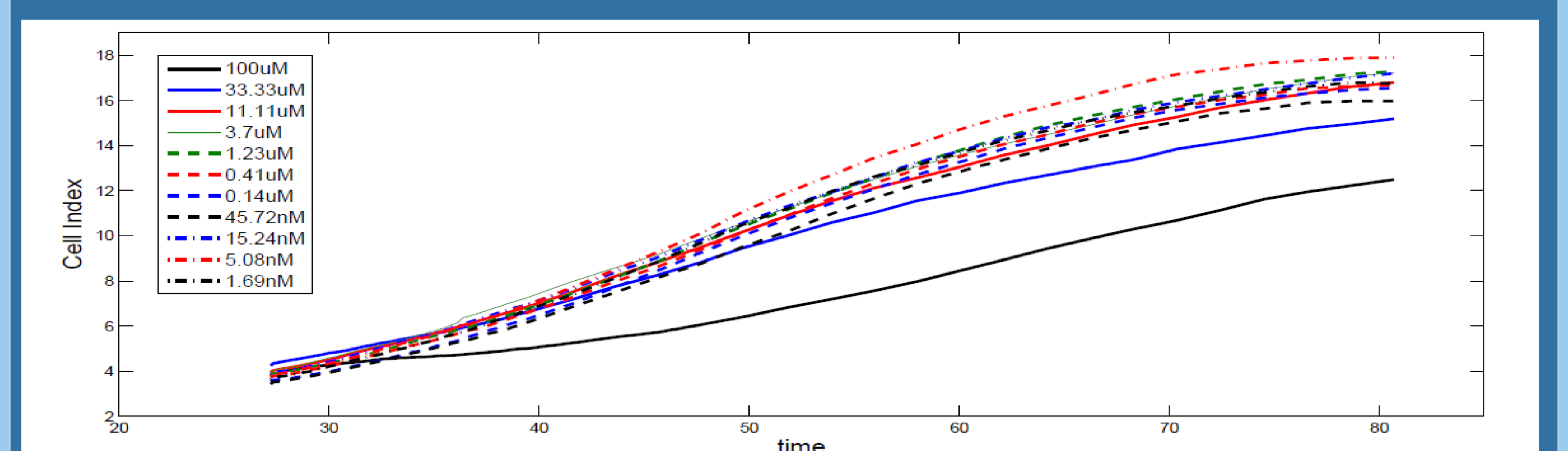


Figure 1. TCRCs for Monastrol

The Deterministic Model

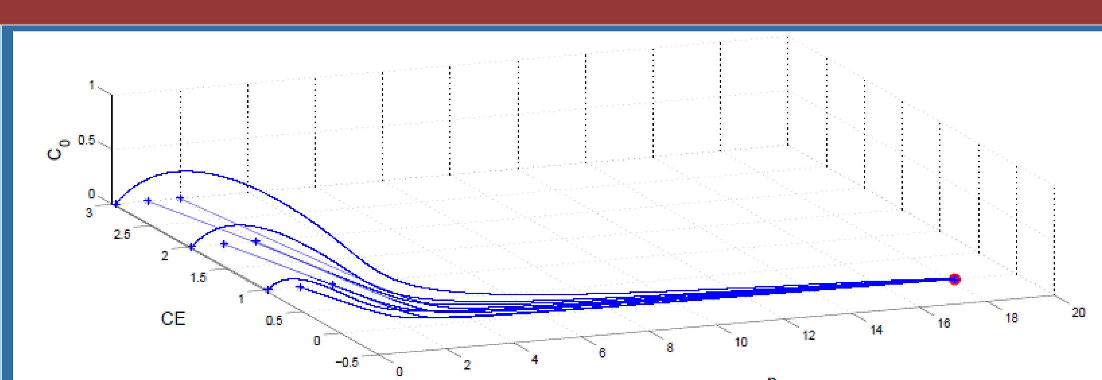
$$\frac{dn(t)}{dt} = \beta_0 n(t)\left(1 - \frac{n(t)}{K_0}\right) - \alpha C_0(t)n(t)$$

$$\frac{dC_0(t)}{dt} = \lambda_1^2 CE(t) - \eta_1^2 C_0(t)$$

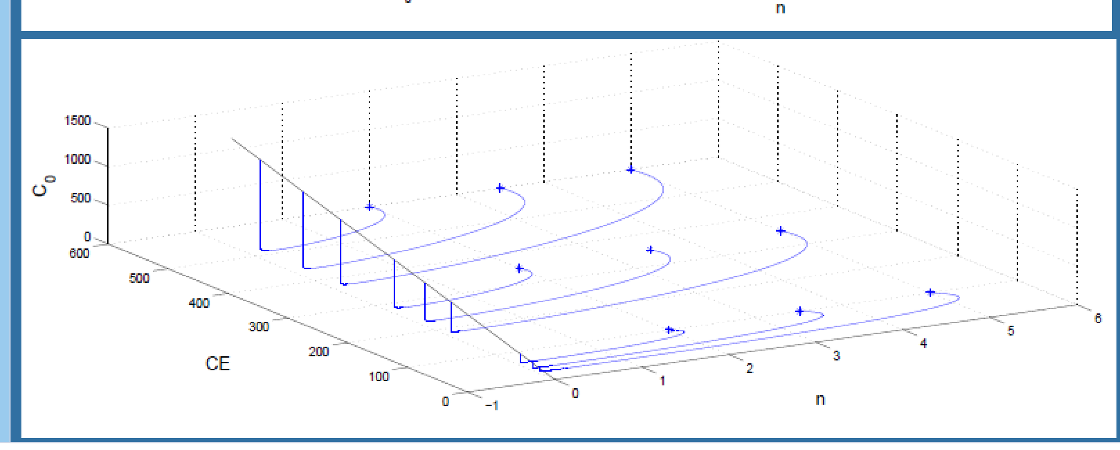
$$\frac{dCE(t)}{dt} = \lambda_2^2 C_0(t)n(t) - \eta_2^2 CE(t)n(t)$$

n(t): cell index at time t
β: cell growth rate
K: capacity volume
$C_0(t)$: internal toxicant concentration at t
CE(t): external toxicant concentration at t
α: toxicant-specific coefficient
λ_1^2: toxicant uptake rate from environment
η_1^2: toxicant input rate to environment
λ_2^2: toxicant uptake rate from cells
η_2^2: loss rate of toxicant absorbed by cells

Bifurcation Analysis



If $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$ and $0 < CE(0) < \frac{\beta\eta_1^2}{\alpha\lambda_1^2}$ the cell index converges to the maximum capacity equilibrium K.



If $\eta_1^2\eta_2^2 - \lambda_1^2\lambda_2^2 > 0$ and $CE(0) > \frac{\beta\eta_1^2}{\alpha\lambda_1^2}$ the cells' population will go to extinction.

Parameter Estimation

Using the Expectation Maximization (EM) algorithm based on the unscented filter (UF), these parameters were estimated from experimental data

Toxicant	Cluster	Beta	K	Eta1	Lamb1	Lamb2	Eta2	Alpha
PF431396	X	0.077	21.912	0.273	0.058	0	0.008	0.238
Monastrol	X	0.074	18.17	0.209	0.177	0.204	0.5	0.016
ABT888	I	0.083	17.543	0.079	0.177	0.205	0.5	0.005

The Stochastic Model

$$\frac{dn(t)}{dt} = \beta_0 n(t)\left(1 - \frac{n(t)}{K_0}\right) - \alpha C_0(t)n(t) + \sigma^2 n(t)dW_t$$

$$\frac{dC_0(t)}{dt} = \lambda_1^2(CE(t) - CE(0)) - \eta_1^2 C_0(t)$$

$$\frac{dCE(t)}{dt} = \lambda_2^2 C_0(t)n(t) - \eta_2^2(CE(t) - CE(0))n(t)$$

Here σ^2 is intensity of noise and W_t is white noise.

Stochastic Bifurcation

- There are two types of stochastic bifurcations: phenomenological and dynamical. We study the phenomenological bifurcations (P-bifurcations), so we search for changes in the shape of the density of the stationary distributions corresponding to the random dynamical system associated with the stochastic model, when the values of the parameters are varied.

•The density of the stationary distribution is a time independent solution of the associated Fokker-Plank equation. Instead of solving the associated Fokker-Plank equation, we obtain numerically a histogram as an estimation of the density of the stationary measure.

•We approximate the solutions using a 2nd order strong Ito-Taylor scheme with time step h = 0.001 and end time T = 50000. To construct projections of the histograms we use indicator functions.

Acknowledgements

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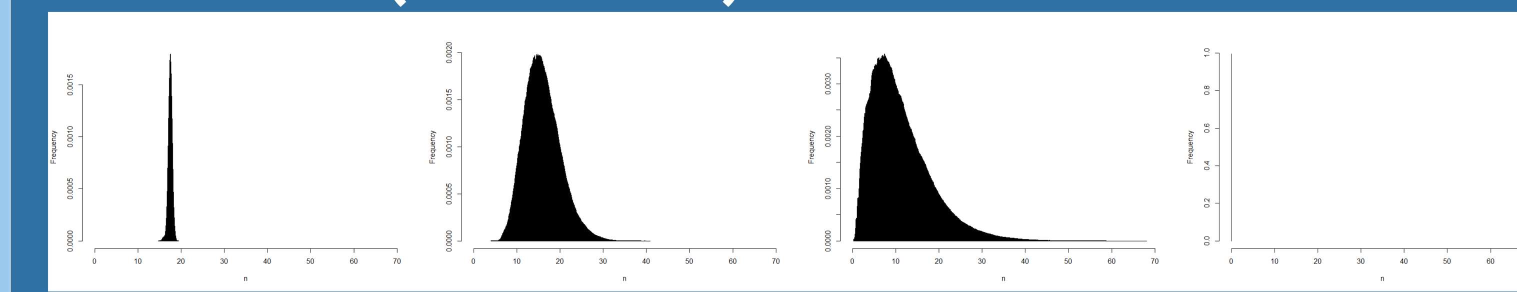
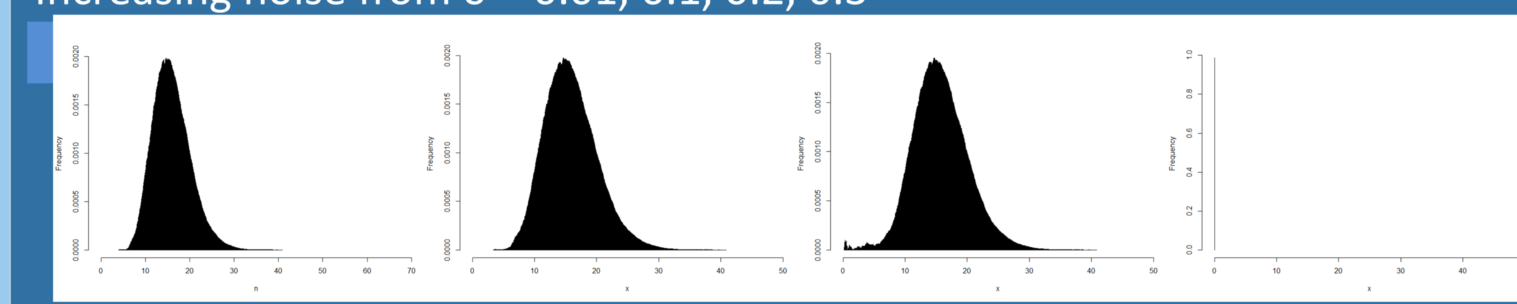
Results

ABT888 (Cluster I)

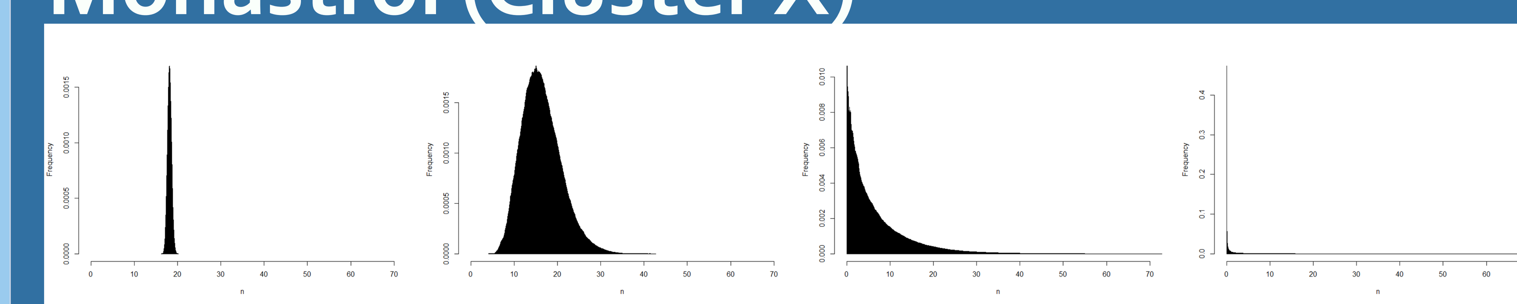


Increasing noise from σ = 0.01, 0.1, 0.2, 0.3

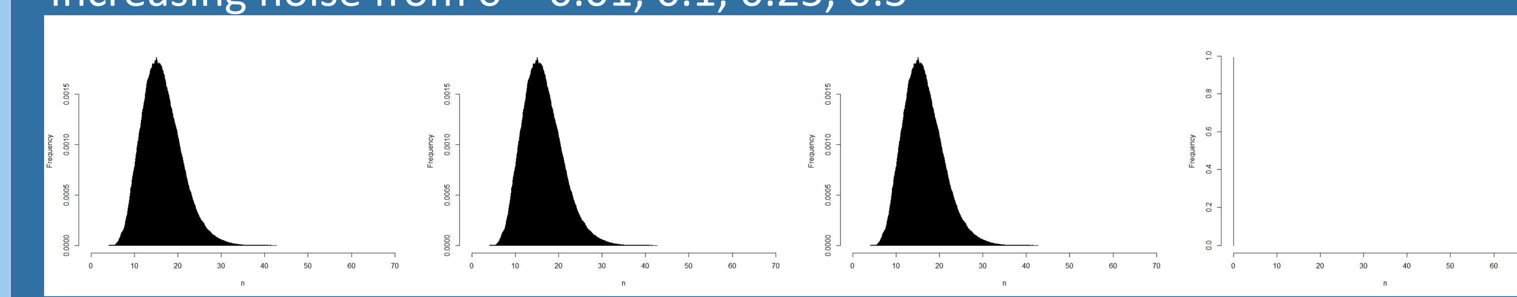


Increasing initial concentration from CE = 125, 300, 330, 340 uM

Monastrol (Cluster X)



Increasing noise from σ = 0.01, 0.1, 0.25, 0.3



Increasing initial concentration from CE = 100, 200, 270, 275 uM

Conclusions

•The cluster type does not have a significant effect on the behavior of the distributions in response to increased noise or initial concentration.

•At first, increasing sigma increases the variance and causes a leftward shift of the distribution. At a certain (high) level of noise, it becomes a Dirac distribution

•Increasing the initial concentration CE(0) does not change the shape of the distribution, until it reaches a high enough concentration such that again becomes a Dirac distribution.

References

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